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The effect of drug lipophilicity and lipid vehicles on the lymphatic absorption of various testosterone esters

T. Noguchi, W.N.A. Charman and V.J. Stella
The University of Kansas, Lawrence, KS 66045 (U.S.A.)

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Summary

Mesenteric lymph was collected from non-restrained unanesthetized rats following oral administration of several different testosterone esters dissolved in various non-polar lipid vehicles.

A good correlation was observed between the differing amounts of the testosterone esters appearing in intestinal lymph (24 h post-dosing) and their respective *n*-heptane/water partition coefficients.

There appeared to be a significant vehicle effect on lymphatic absorption when monitoring the lymphatic transport of testosterone undecanoate after its oral administration in various lipid vehicles. Lymphatic absorption of testosterone undecanoate was greatest when administered in oleic acid ($C_{18:1}$) and long-chain unsaturated triglyceride vehicles. However, mixtures of oleic acid–monoolein (representing a synthetic digestion mixture of a triglyceride) failed to improve, and in fact decreased, the lymphatic absorption of testosterone undecanoate relative to an oleic acid vehicle.

Although the extent of lymphatic absorption of testosterone undecanoate was very small, it did appear to be the major determinant of the bioavailability of orally administered testosterone undecanoate.

Correspondence: V.J. Stella, School of Pharmacy, University of Kansas, Lawrence, KS 66045, U.S.A.

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Introduction

The mechanisms whereby lipophilic molecules are absorbed from the gastrointestinal tract and transported to the general circulation are complex and poorly understood (Patton, 1981).

Triglycerides, for example, undergo initial lipolysis in the intestinal lumen to the corresponding fatty acids and monoglyceride and these entities are absorbed into the epithelial cells of the gut. The triglyceride is then resynthesized in the epithelial cells and is ultimately transported as the major component of chylomicrons which are the lipoidal transport system of the intestinal lymphatics.

As most lipophilic molecules which are transported in the lymph reside in the triglyceride core of the chylomicron fraction (Sieber et al., 1974) of the intestinal lymph, we have used a series of long-chain acyl esters of testosterone in order to investigate the effect of the lipophilicity of a molecule on its intestinal lymphatic transport. The properties of the particular vehicle in which the drug is administered appear to effect the extent of lymphatic absorption (Palin et al., 1982). Therefore, we have evaluated a number of lipid vehicles in order to confirm whether or not there are specific vehicle effects governing the lymphatic absorption of lipoidal molecules.

Materials and Methods

The chemicals used in this study were testosterone, testosterone acetate, testosterone heptanoate and safflower oil (Sigma Chemicals, St. Louis, MO 63178), testosterone undecanoate (Research Plus Steroid Laboratories, Danville, NJ 07834), oleic acid (Fischer Scientific, Fair Lawn, NJ 07410), monoolein (Myverol 18-92, Eastman Kodak, Rochester, NY 14650), Intralipid 10% (Cutter Laboratories, Berkeley, CA 94710), Neobee M-5 (medium chain triglyceride) and Max EPA ($C_{18:2}$-$C_{20:3}$ rich fish oils) from R.P. Scherer, Clearwater, FL 33518.

Synthetic procedures

Testosterone palmitate and testosterone oleate were synthesized in our laboratory by a standard procedure (Gould et al., 1957). Testosterone oleate was purified by silic acid column chromatography and eluted with chloroform–ethyl acetate (4 : 1). Testosterone palmitate was purified by washing with 10% $NaHCO_3$, then water until neutral, and was subsequently recrystallized from methanol. Both compounds were of > 99% purity as determined by HPLC. The elemental analysis of both compounds were as follows: testosterone palmitate; found C: 80.15, H: 11.43; calc. C: 79.99, H: 11.10, testosterone oleate; found C: 80.08, H: 11.30; calc. C: 80.04, H: 10.94.

Animal experiments

The mesenteric lymph duct of male Sprague-Dawley rats, weighing 270–370 g, was cannulated after 24 h fasting by our previously described method (Noguchi et al., 1985). Lymph was collected for 24 h after oral administration of the drug

dissolved in an oily vehicle to unanesthetized rats by gavage with a feeding needle and syringe. When required, the animal was lightly anesthetized with ether and 0.5-ml blood samples were taken from the ophthalmic plexus.

Portal blood levels of testosterone were measured by cannulating the portal vein with polyethylene tubing (SP 31, Dural Plastics and Eng., Dural, N.S.W. 2158, Australia). In this study, rats were anesthetized with sodium pentobarbital (40 mg/kg, i.p.) throughout the experiment. Testosterone or testosterone undecanoate was injected intraduodenally to each rat at a dose equivalent to 7.5 mg of testosterone in 100 μl of oleic acid.

In vitro stability studies of the various testosterone esters were performed by adding 12 μg testosterone equivalents of the esters, dissolved in 20 μl of Intralipid, to 1.5 ml of rat plasma. These samples were incubated at 31.5°C and the disappearance of the ester, and formation of testosterone, was followed for 6 h by appropriate HPLC analysis.

Assay method for testosterone esters

Assay methods for the various testosterone esters were essentially the same except for minor variations in the mobile phases and internal standards used in the chromatographic analysis. A 100-μl aliquot of an internal standard solution was added to either 0.1 ml of lymph or plasma and the testosterone ester and the internal standard were extracted with 5 ml of freshly distilled ether. After freezing the aqueous layer in dry-ice–acetone, the ether layer was decanted into a centrifuge tube and the ether evaporated under a gentle stream of nitrogen gas. The residue was resuspended in 0.2 ml of 5% (w/v) sodium chloride solution and the testosterone ester was extracted with 0.1 ml of cyclopentanone. An aliquot of the cyclopentanone solution was subjected to HPLC analysis under the following conditions; pump

TABLE 1

MOBILE PHASES, INTERNAL STANDARDS AND RETENTION VOLUMES FOR THE CHROMATOGRAPHIC ANALYSIS OF THE TESTOSTERONE ESTERS

Compound	Mobile phase	Internal standard	Retention volume [a]	
			Drug	I.Std.
Testosterone	acetonitrile/ water (60 : 40)	testost. acetate	7.6	11.6
Testosterone heptanoate	THF/water/ acetonitrile (30 : 25 : 45)	testost. undecanoate	11.4	17.6
Testosterone undecanoate	as above	testost. heptanoate	17.6	11.4
Testosterone palmitate	methanol	testost. undecanoate	17.2	7.6
Testosterone oleate	methanol	as above	16.8	7.6

[a] ml of mobile phase

model 110A, UV detector model 153 (Beckman, Berkeley, CA 94710, U.S.A.), Lichrosorb 10 RP 18 analytical column 4.6 mm × 25 cm (Chrompack, The Netherlands), Lichrosorb guard column 2.1 mm × 3 cm (Brownlee, Santa Clara, CA 95050, U.S.A.). The mobile phases and internal standards that were used are described in Table 1.

Results and Discussion

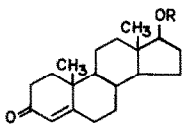
Testosterone esters

Testosterone, an androgenic steroid hormone, undergoes significant presystemic clearance following oral administration and consequently has negligible oral bioavailability (Nieschlag et al., 1975). The lymphatic absorption of testosterone per se has been previously studied (Sieber et al., 1974) and shown to be minimal. The promotion of the lymphatic absorption of testosterone, or a suitable lipophilic prodrug, would bypass initial presystemic clearance and afford enhanced oral bioavailability.

Coert et al. (1975) demonstrated the exclusive absorption of testosterone undecanoate by the intestinal lymphatics following oral administration, and this particular testosterone ester has been found to be pharmacologically active after subcutaneous injection to rats (Gould et al., 1957).

The series of esters shown in Fig. 1 were utilized to investigate the effect of a molecules' lipophilicity on its ultimate lymphatic absorption. Fig. 2 describes the time course of the lymphatic transport of total testosterone (ester and free

Fig. 1.



R=H TESTOSTERONE
R=COC_6H_{13} T.HEPTANOATE
R=$COC_{10}H_{21}$ T.UNDECANOATE
R=$COC_{15}H_{31}$ T.PALMITATE
R=$COC_7H_{14}CH=CHC_8H_{17}$ T.OLEATE

Fig. 2.

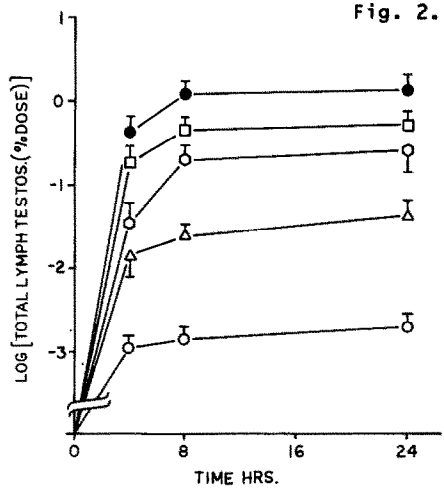


Fig. 1. The structure of testosterone and the four esters used in this study.

Fig. 2. The logarithm of the total testosterone appearing in mesenteric lymph (as testosterone equivalents expressed as % of dose administered) as a function of time. ●–●, T. palmitate; □–□, T.undecanoate; ○–○, T.oleate; △–△, T.heptanoate; ○–○, testosterone.

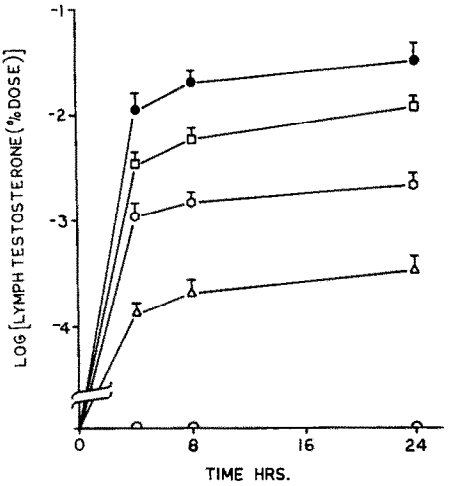


Fig. 3. The logarithm of free testosterone appearing in mesenteric lymph (as % dose administered) as a function of time. ●–●, T. undecanoate; □–□, T.heptanoate; ○–○, testosterone; △–△, T. palmitate; ○–○, T. oleate.

testosterone) after oral administration as 15 mg equivalents of testosterone in 200 μl of oleic acid. As the alkyl chain of the testosterone ester was increased, the extent of lymphatic absorption increased accordingly (except for the oleate ester).

Only small quantities of free testosterone were recovered in the lymph, with the major lymphatic transport form of testosterone being as the ester. In the case of the palmitate and oleate esters, the total amount of free testosterone appearing in the lymph was less than when free testosterone itself was administered and this is described in Fig. 3. This finding is consistent with the results of an in vitro stability study of the testosterone esters using rat plasma where the formation of free testosterone from the corresponding ester was only observed after the incubation of the heptanoate and undecanoate esters of testosterone [1].

Therefore, providing that cleavage of the ester bond is a prerequisite for pharmacological activity, testosterone undecanoate, appeared to be the most promising candidate as a lipophilic testosterone prodrug from the standpoints of both the extent of total lymphatic absorption and the rate of prodrug cleavage. Furthermore, it has been reported that testosterone esters may have intrinsic pharmacological activity in rat brain (Kishimoto, 1973), and even longer chain, more lipophilic, unsaturated testosterone esters may prove useful.

[1] The apparent half-lives for the appearance of testosterone from the undecanoate and heptanoate esters of testosterone when incubated in rat plasma were approximately 1.5 and 2 h, respectively. The appearance of testosterone was not observed after the plasma incubation of the palmitate or oleate esters. Other in vivo sites of cleavage of these esters in addition to the plasma, may be present in the body, although this possibility was not determined.

The relationship between the extent of lymphatic appearance of total testosterone (free plus ester form) and their respective log P (*n*-heptane/water) values of the esters is described in Fig. 4. The partition coefficients of the differing esters were calculated from literature data (Hansch and Leo, 1979). A good linear correlation was obtained between the extent of lymphatic transport and the partition coefficient of the saturated alkyl esters of testosterone suggesting that the lipophilicity of a molecule, as indicated by partition coefficient, is a major determinant of the extent of its ultimate lymphatic transport, consistent with the work of Sieber (1976). The correlation coefficient for the analysis of testosterone and the three saturated esters was $r = 0.982$. When analyzing this relationship with respect to the oleate ester, the correlation coefficient decreased to $r = 0.929$. This apparent discrepancy in the lymphatic transport–partition coefficient relationship may be attributed to the unsaturation in the acyl chain of the oleate ester leading to conformational changes in the molecule that may well effect its ultimate lymphatic transport. If a linear relationship was assumed between partition coefficient and lymphatic transport of the testosterone esters, very high log P values of greater than 10 would be necessary in order to achieve significant lymphatic absorption (assumed to be greater than 10% of the administered dose) and therefore systemic delivery.

Vehicle effects

To investigate the existence of vehicle effects on lymphatic absorption, testosterone undecanoate was chosen as a model compound as it showed promise as a lymphatically absorbed bioreversible lipophilic derivative of testosterone. Testosterone undecanoate was orally administered in 200 μl of the various lipoid vehicles listed in

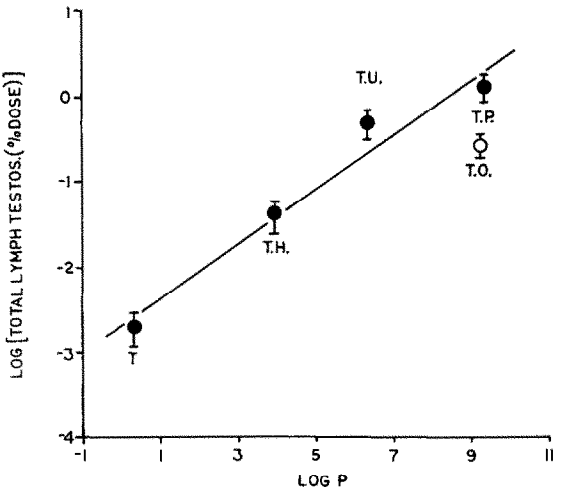


Fig. 4. Relation between the logarithm of total testosterone equivalents appearing in 24 h mesenteric lymph (mean ± S.E.M., as % dose administered) and the logarithm of their respective *n*-heptane/water partition coefficients. T.P., T.palmitate; T.O., T.oleate; T.U., T.undecanoate; T.H., T.heptanoate; T, testosterone.

TABLE 2

APPEARANCE OF TOTAL TESTOSTERONE IN 24 h FISTULATED MESENTERIC LYMPH. TESTOSTERONE UNDECANOATE WAS ADMINISTERED ORALLY AS 15 mg TESTOSTERONE EQUIVALENTS IN 200 μl OF THE LISTED LIPID VEHICLES

Lipid vehicle	Lymphatic appearance of total testosterone (% dose/24 h) [a]
Oleic acid	0.50 ± 0.14
Peanut oil	0.45 ± 0.14
Safflower oil	0.45 ± 0.08
Max EPA	0.21 ± 0.08 [b]
Oleic acid/monoolein (1 : 1 v/v)	0.21 ± 0.05 [b]
Oleic acid/monoolein (2 : 1 v/v)	0.15 ± 0.07 [b]
Intralipid	0.18 ± 0.01 [b]
Neobee M-5	0.09 ± 0.01 [b]

[a] Mean ± S.E.M. for $n > 4$.

[b] Significantly different from oleic acid at $0.05 < P < 0.1$ by Student's t-test.

Table 2 where the respective % of dose transported are also tabulated. The time course of % dose transported is shown in Fig. 5. If the testosterone undecanoate remains associated with lipoidal phases during the digestion of the lipid vehicle and the subsequent absorption of the resulting digestion products, which is not unlikely based on consideration of the log P values of the esters and the "hydrocarbon

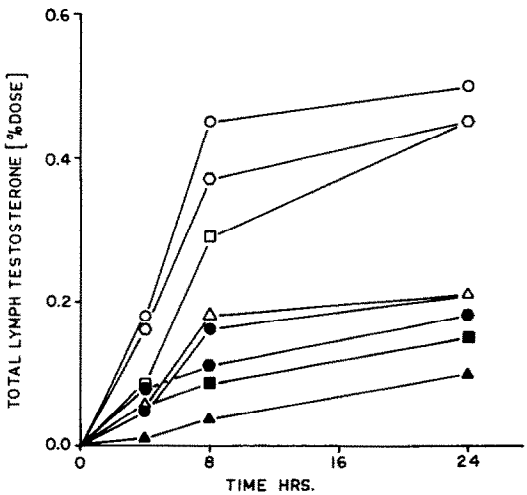


Fig. 5. Total lymph testosterone, as percent of dose of testosterone undecanoate administered, appearing in mesenteric lymph as a function of the differing lipid vehicles. Dose was 15 mg equivalents of T.undecanoate per 200 μl lipid vehicle. ○–○, oleic acid; ○–○, safflower oil; □–□, peanut oil; △–△, oleic acid/monoolein (1 : 1); ●–●, Max EPA; ●–●, oleic acid/monoolein (2 : 1); ■–■, intralipid; ▲–▲, Neobee M-5.

continuum" described by Patton (1981), then the quantity of drug transported via the lymph may well be lipid vehicle-dependent. The rates (% dose transported per unit time) and the extent of transport of the model compound, described by Fig. 5, were not significantly different between the oleic acid ($C_{18:1}$), safflower oil (76% $C_{18:2}$; 14% $C_{18:1}$) and peanut oil (56% $C_{18:1}$; 26% $C_{18:2}$) vehicles. This is not surprising as long-chain fatty acids per se, or those arising from the lipolysis of the corresponding triglyceride, are absorbed to a greater extent by the intestinal lymphatic system rather than via the portal blood (Gangl and Ockner, 1975, McDonald et al., 1980). The portal blood transport of orally administered fatty acids appears to increase as the chain length of the fatty acid decreases. Subsequent to absorption from the lumen, long-chain fatty acids are resynthesized to the corresponding triglycerides which are then incorporated into, and transported by chylomicrons. Medium- or short-chain fatty acids are poorly transported by the lymphatic system as they are not incorporated to any significant extent in the chylomicrons. Consequently, long-chain fatty acids are better absorbed by the lymphatic system than are medium- or short-chain fatty acids. The lower lymphatic transport of testosterone undecanoate when administered in Neobee M-5, the medium-chain triglyceride vehicle which on lipolysis would liberate medium-chain fatty acids, is probably due to decreased lymphatic transport, via chylomicrons, of medium chain fatty acids. McDonald et al. (1980) reported a decreased lymph transport/portal blood transport ratio for C_{18} fatty acids of increasing degrees of unsaturation. This is consistent with the decreased lymphatic transport of testosterone undecanoate when it was administered in the highly unsaturated fatty acids that constitute the Max EPA lipid vehicle. The possibility of a direct relationship between the degree of lipid vehicle unsaturation and the subsequent lymphatic transport of co-administered lipophilic drugs is somewhat tentative at this point, and represents an area of research that requires clarification.

Interestingly, the synthetic triglyceride digestion mixtures consisting of oleic acid/monoolein appeared to decrease the lymphatic transport of testosterone undecanoate relative to the oleic acid vehicle. While there is some literature precedence for an in vitro inhibitory effect of monoglycerides on eventual phosphatidylcholine biosynthesis required for chylomicron stabilization (Polheim et al., 1973), there are sufficient in vivo examples that suggest little effect in the intact animal (Charman et al., 1985; Shaikh and Kuksis, 1983). The mechanism by which the co-administered monoglyceride decreased the lymphatic transport of the testosterone undecanoate is unknown and was not investigated in the present study. It should be noted that the monoglyceride isomer used in this study was the more thermodynamically stable 1-monoglyceride, as opposed to the 2-monoglyceride. The 2-monoglyceride is the major isomer produced in vivo during fat digestion, although subsequent isomerization does occur. Although the liquid crystalline phase properties of the two isomers may differ (Ljusberg-Wahren et al., 1983), the inhibitory effects of the two isomers on in vitro phosphatidic acid production are similar (Polheim et al., 1973).

Vehicle volume effects

The effect of vehicle volume (oleic acid) on the lymphatic appearance of

Fig. 6.

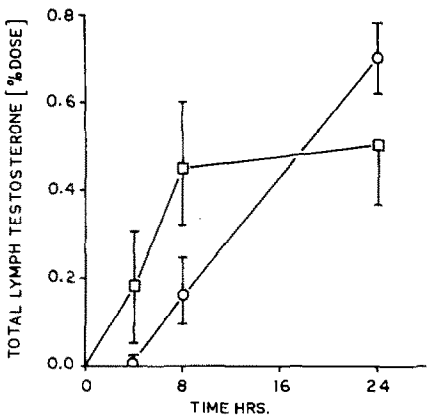


Fig. 7.

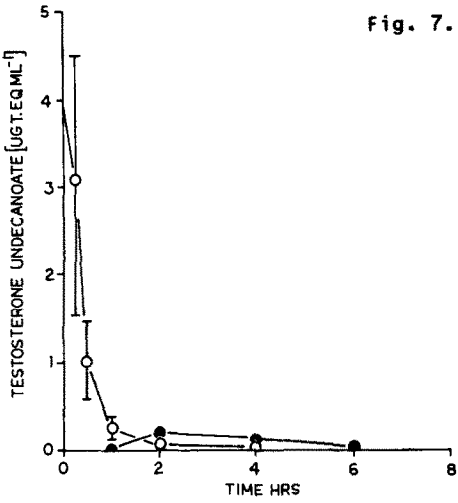


Fig. 6. Effect of vehicle volume of oleic acid on the lymphatic appearance (mean ± S.E.M.) of 15 mg equivalents of testosterone undecanoate administered orally. O–O, 500 μl; □–□, 200 μl.

Fig. 7. Systemic plasma levels of testosterone undecanoate (μg testosterone equiv./ml plasma) as a function of time and route of administration. O–O, i.v. dose of 245 μg testosterone equiv./0.4 ml Intralipid/rat; ●–●, oral dose of 15 mg testosterone equiv./200 μl oleic acid. F calculated as $(AUC_{oral}/D_{i.v.})/(AUC_{i.v.}/D_{oral})$.

testosterone undecanoate is described in Fig. 6. After an initial lag time of approximately 4 h for the initiation of drug transport from the 500-μl dose volumes, the rate of lymphatic drug transport was then similar to that found with the 200-μl dose volumes. The rate of lymphatic appearance of the drug is possibly controlled somewhat by the size of the lipid reservoir in the intestinal cells, the existence of which was shown by Friedman et al. (1972). When a large volume (500 μl/rat) of the oleic acid solution was administered orally, lymphatic transport of the drug was significantly delayed when compared with the administration of the smaller volume (200 μl/rat) of oleic acid. This may be due to a prolonged gastric emptying time and/or the saturation of a process(es) involved in the lymphatic transport of lipophilic molecules from the lumen of the gut, via the intestinal epithelial cells, to the lymphatic system. On going studies of the kinetics of lymphatic transport are currently underway.

Bioavailability studies

As can be seen in Fig. 2, only 0.5% of the administered dose of the testosterone undecanoate was collected in the fistulated lymph [2]. This might be partially due to

[2] Studies by Horst et al. (1976) have shown that a 5-α reduction of testosterone undecanoate occurs in the lumen of the intestine and that this reduced compound is transported in the intestinal lymph. It accounts for approximately 20% of the testosterone equivalents isolated from intestinal lymph. The 5-α compound appears to be pharmacologically active and as such our measurements of testosterone undecanoate bioactivity, based on the parent drug bioavailability, are conservative.

effects of the surgical intervention necessary to estimate lymphatic absorption and may not indicate the true amount of intact testosterone undecanoate absorbed via lymphatics in the intact rat. Less than 1% of the dose of testosterone undecanoate (largely as the ester itself) was recovered from intestinal contents and gut homogenates 24 h after oral dosing. A study was designed to estimate the systemic bioavailability of orally administered testosterone undecanoate. By comparing this value with the quantity of drug recovered in the fistulated mesenteric lymph, an indication as to whether or not the surgery necessary for estimating lymphatic transport effects the quantities of drug transported in the lymph can be gained. Consequently, sham-operated animals were not used in the intravenous study. The systemic plasma levels of testosterone undecanoate after its oral and intravenous administration in Intralipid are shown in Fig. 7. The rapid clearance of the testosterone ester after intravenous administration ($t_{0.5}$ approximately 20 min) may be due to the clearance kinetics of the administered emulsion; however, the plasma concentration profile of testosterone undecanoate is consistent with the literature (Hobbelen et al., 1975) where the ester was injected intravenously after being dissolved in rat serum. As the plasma concentration of testosterone undecanoate was below the detection limit of the assay after 4 h, further data points were not obtained. There was a tendency for slower "apparent" plasma disappearance of testosterone undecanoate after oral administration. The apparent $t_{0.5}$ life calculated from the terminal portion of the plasma–time profile from the orally administered undecanoate ester was approximately 100 min which suggests slow entry of the drug into the systemic circulation (i.e. a flip-flop situation may have occurred). This is consistent with significant lymphatic absorption. Comparison of calculated AUC_0^{6h} values using the trapezoidal method, corrected for dose differences, for oral versus intravenous administration of testosterone undecanoate gave an estimated bioavailability of 0.39%. By comparing this value to the 0.5% of administered testosterone undecanoate collected in the intestinal lymph following oral administration, it appears that only the fraction of the testosterone undecanoate transported by the intestinal lymphatic system reached the systemic circulation intact.

The time-dependent levels of free testosterone appearing in portal blood follow-

TABLE 3

PORTAL PLASMA TESTOSTERONE LEVELS (μg/ml TESTOSTERONE EQUIV.) FOLLOWING INTRADUODENAL ADMINISTRATION OF EITHER TESTOSTERONE OR TESTOSTERONE UNDECANOATE. DOSE WAS 7.5 mg TESTOSTERONE EQUIVALENTS/100 μl OF OLEIC ACID

Time (min)	Portal testosterone level (μg/ml) [a] following administration of either	
	Testosterone	Testosterone undecanoate [b]
10	1.47 ± 1.22	0.14 ± 0.01
30	3.47 ± 0.33	0.19 ± 0.02
60	6.60 ± 2.21	0.27 ± 0.07

[a] Mean ± S.E.M. for $n > 4$.

[b] No detectable levels of testosterone undecanoate appeared in the portal blood.

ing the intraduodenal administration of either free testosterone or testosterone undecanoate are shown in Table 3. The level of testosterone appearing in portal blood 1 h after the intraduodenal administration of the undecanoate ester, 0.27 μg/ml, was significantly less than the 6.60 μg/ml level of free testosterone in portal blood following the intraduodenal administration of free testosterone. Therefore, the low oral bioavailability of the prodrug does not appear to be due to the metabolism of testosterone undecanoate by the liver as it was not found to be transported in portal blood, and only low concentrations of free testosterone were detected in portal blood after the intraduodenal administration of the ester. In the case of testosterone undecanoate, its administration in a lipid vehicle appeared insufficient to overcome the metabolic clearance of the prodrug in the lumen or the epithelial cells of the intestine. Thus, it appears that administered testosterone undecanoate undergoes extensive prehepatic clearance and only the unmetabolized portion of the administered testosterone undecanoate is transfered to the systemic circulation via the intestinal lymphatic system.

Acknowledgements

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